ExAct

Excipients & Actives for Pharma

No. 10, May 2003

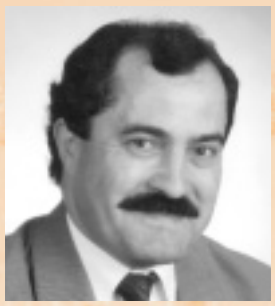
Dear Reader,

Numerous drugs that are marketed as solid oral dosage forms are available in many different potencies. The easiest way of producing a range of these is to develop formulations using the cost-saving method of direct compression processing. The Ludipress® range comprises excipients that satisfy the specific characteristics of individually tailored dosage forms.

Lozenges and effervescent tablets must dissolve quickly and should not leave any residue. Ludipress® LCE does not contain the disintegrant Kollidon® CL; it is therefore completely soluble in water and thus particularly suitable for this application. Co-formulated with Kollidon® CL as disintegrant, Ludipress® LCE also demonstrates its suitability for fast-disintegrating tablet formulations.

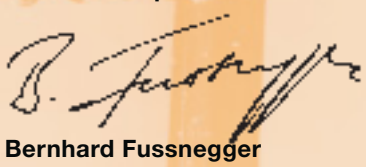
Since its introduction in 1999, Ludipress® LCE has found its way into various registered products worldwide.

The article on pages 2 to 3 highlights the properties of Ludipress® LCE as an excipient for efficient tablet production.



Yours sincerely,

BASF Aktiengesellschaft
Strategic Marketing
Pharma Excipients



Bernhard Fussnegger

Content

Imprint

Publisher:
BASF Aktiengesellschaft

Editorial staff:
Dr. Volker Bühler, Valérie Filiatreau, Dr. Hubertus Folttmann, Dr. Bernhard Fussnegger, Dr. Karl Kolter, Dr. Jan-Peter Mittwollen, Dr. Anisul Quadir, Dr. Thorsten Schmeller, Silke Werth

Concept/Layout:
MLW KommunikationsForm GmbH Werbeagentur, Mannheim

Print:
Knopf druck + media, Edingen-Neckarhausen

BASF

ExAct
Excipients & Actives for Pharma

Ludipress® LCE

A new direct compression excipient.

K. Kolter, R. Heinz, B. Fussnegger

› Introduction

Ludipress® LCE, a new direct compression excipient based on 96.5 % lactose and 3.5 % povidone (Kollidon® 30), is manufactured via a special agglomeration process to achieve a compound with good compression properties connected with an excellent blending behavior. Direct compression of low dosed drugs is often prohibited due to segregation of powder blends. Currently this remains a problem in the pharmaceutical industry **[1].**

SEM-photo of Ludipress® LCE ***(Figure 1)***

› Objective

The objectives of this study were
1. to characterize the new direct compression excipient Ludipress
2. to correlate the powder properties with the properties of tablets
3. to check the suitability for manufacturing low dosed tablets.

› Materials and Methods

Materials

Ludipress® LCE (BASF AG), glibenclamide micronized (Arzneimittelwerk Dresden), magnesium stearate (Bärlocher).

Apparatus

Korsch PH 106 rotary press with compression research system (Korsch Pressen GmbH), Turbula blender T2C (Bachofen AG).

Powder characteristics

Particle size (sieve tower with calculation according to RRSB), particle size (laser diffraction), flowability (angle of repose and flow time with Pfrengle funnel), water sorption (sorption profile), amorphous lactose (differential scanning calorimetry), granule and surface structure (scanning electron microscopy).

Tablet properties

Hardness
Friability
Standard deviation of mass
Content uniformity
(tablet dissolved in 0.1-N NaOH, filtered and measured at 300 nm).

Tabletting

Ludipress® LCE tablets:

Ludipress® LCE was blended with magnesium stearate (0.5 %) for 10 minutes and compressed at increasing compression forces to give tablets of 10 mm diameter and 300 mg weight.

Glibenclamide tablets:

Ludipress® LCE, glibenclamide (1.0 %, 0.5 %, 0.1 %), Kollidon magnesium stearate (0.5 %) were sieved through 0.8 mm, blended for 10 minutes and compressed to give tablets of 8 mm diameter and 200 mg weight.

› Results

The powder properties of Ludipress® LCE are summarized in **table 1.** The mean particle sizes determined by sieve analysis and laser diffraction correspond to each other. Both methods show a narrow particle size distribution. After drying at 105 °C most of the water was bound as monohydrate, since the relative humidity of the powder was comparably low and the water sorption profile indicated nearly no water uptake up to 75 % r. h. This low water uptake in humid atmosphere led to the conclusion

Powder properties of Ludipress® LCE ***(Table 1)***

Angle of repose	29.5°
Flow time (150 ml)	6.9 s
Mean particle size (sieve tower) d'	260 µm, slope n 1.85
Mean particle size, D[4.3]	275 µm, span 1.75
Loss on drying (105 °C)	5.75 %
Relative humidity	20.1 %
Bulk density	0.57 g/ml
Hausner ratio	1.19
Water sorption 28 d/33 % r. h.	-0.34 %
28 d/66 % r. h.	0.13 %
28 d/75 % r. h.	0.52 %

Properties of glibenclamide tablets ***(Table 2)***

	Weight		Content uniformity		
Glibenclamide	Average [%]	SD [%]	Content [%]	SD [%]	USP/Ph. Eur.
2 mg/1 %	100.30	0.56	101.69	1.29	fulfilled
1 mg/0.5 %	100.42	0.84	99.19	1.06	fulfilled
0.2 mg/0.1 %	102.03	1.42	101.19	2.15	fulfilled

ExAct
Excipients & Actives for Pharma

that there is no amorphous lactose in this compound, which was secured by DSC measurements.

Ludipress® LCE consists of porous granules which are able to be deformed under pressure. The compression force-hardness profile exhibits a nearly linear increase up to 300 MPa equivalent to 25 kN for a 10 mm tablet. Friability was zero and the relative standard deviation of mass was between 0.4 and 0.7%. These excellent compression properties can be explained by the furrowed surface structure, which causes strong interlocking of the compressed granules. Additionally, the effective binder povidone contributes to the hardness as it binds the fine lactose particles together **(figure 2).** If the compression speed is increased, most excipients produced tablets with reduced hardness. This could not be detected with Ludipress® LCE. The hardness of glibenclamide tablets remained at the same level **(figure 3).**

Due to the furrowed surface structure, Ludipress® LCE produces interactive mixtures with active ingredients, which do not segregate. This was visualized using fine cacao powder as colorant (10 %) after blending for 10 min. The difference in the blending behavior of Ludipress® LCE and crystalline lactose can be seen clearly **(figure 4).**

The suitability for dosage forms with a low drug dose was proven in glibenclamide tablets with a content of 1.0 %, 0.5 % and 0.1 % active. All formulations fulfilled the requirements of USP and Ph. Eur. The standard deviation of content uniformity was 0.3–0.8 % higher than the standard deviation of mass. This is an extremely positive value, especially when the simple blending process is taken into consideration.

› **References**
[1] A. Armstrong, Pharm. Tech. Eur. 1997 (9), 24–30.

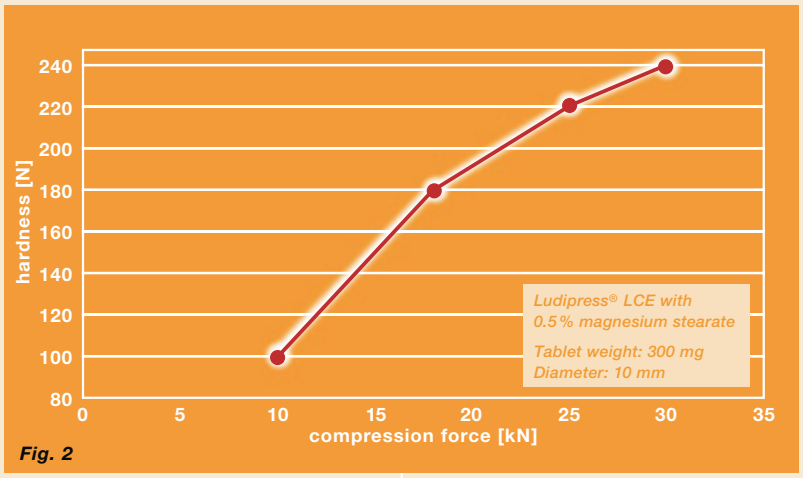


Fig. 2

Compression force-hardness profile of Ludipress® LCE ***(Figure 2)***

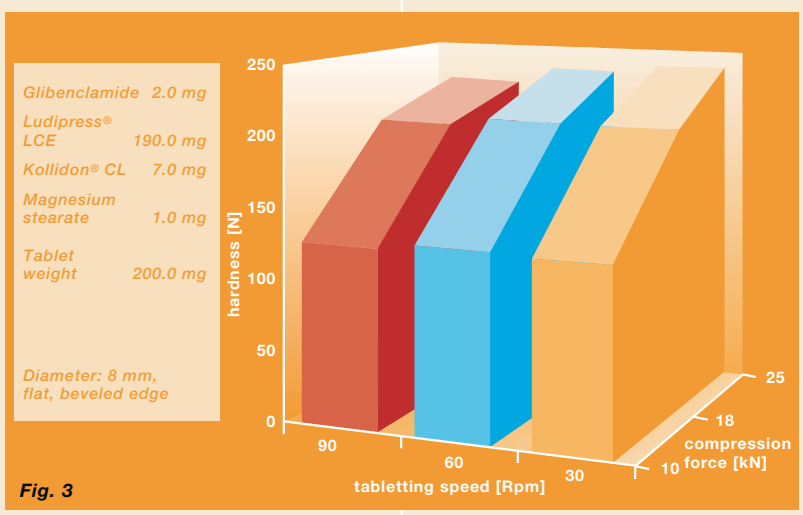


Fig. 3

Influence of compression speed on hardness of glibenclamide tablets ***(Figure 3)***

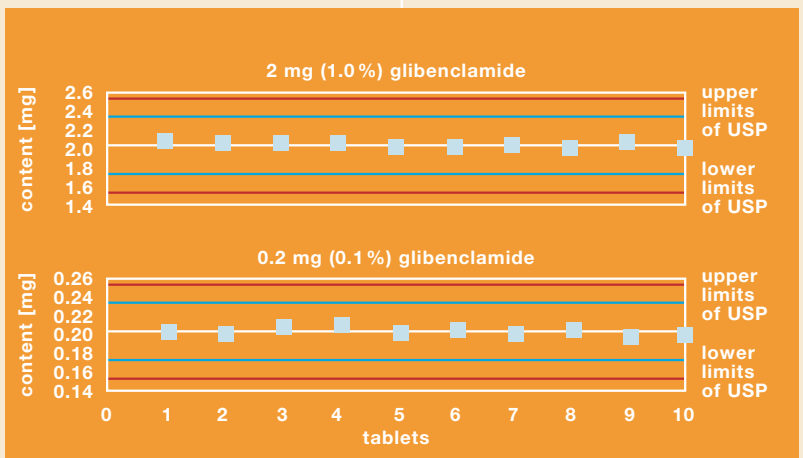


Fig. 5

Photos of blends with cacao powder (10 %) ***(Figure 4)***

Lactose

Ludipress® LCE

Content uniformity of glibenclamide tablets ***(Figure 5)***

› **Conclusions**
› Ludipress® LCE can be characterized as a direct compression excipient combining excellent flowability with outstanding blending and compression properties.
› Tablet properties like hardness, mass deviation and content uniformity can be explained by the powder characteristics especially the granule and surface structure.
› Ludipress® LCE is especially suitable for the manufacturing of low dosed drugs by direct compression.

ExAct
Excipients & Actives for Pharma

Kollidon® SR

Sustained release formulations of different drugs.

T. Steenpaß, T. C. Rock, K. Kolter

Composition of tablets [mg] and tablet characterisitics ***(Table 1)***

› Introduction

From an economical point of view the production of sustained release tablets by direct compression is of great promise. An innovative excipient that offers good controlled release characteristics together with excellent direct compression properties is required as the essential tool for the development and manufacture of matrix tablets **[1, 2].**

› Objective

In this respect Kollidon® SR was developed as a free-flowing non hygroscopic powder consisting of polyvinyl acetate (8 parts w/w) and polyvinylpyrrolidone (2 parts w/w). A convincing excipient is expected to be easily applicable for a broad selection of different drugs. In this study Kollidon® SR-based sustained release tablets similar to market products of different drugs are represented **[3].**

› Materials and Methods

Materials

Kollidon® SR (BASF AG);
Tramadol-HCl (Chemagis Ltd.);
Diltiazem-HCl (Farmacon);
Diclofenac-Na (Irotec);
Aerosil 200 (Degussa);
Magnesium stearate (Bärlocher).

Powder properties

Measurement of angle of repose and flow time with a Pfrengle funnel.

Tabletting

Blending for 10 minutes in a turbula mixer, compressing by use of an instrumented Korsch EK0 single-punch press, tablet diameter 10 mm, beveled edge.

Tablet properties

Determination with a Krämer tablet tester (HT-TMB), friability with an Erweka Friabilator.

Release studies

According to the USP XXIII method by use of a Pharmatest PTW-S dissolution tester, 50 rpm, paddle, 37 °C, 0.08 N HCl (0–2 h), change to pH 6.8 phosphate buffer (2–16 h); release study for the diclofenac-Na formulation pH 6.8 phosphate buffer (0–16 h); spectrophotometrical determination of drug release.

› Results and Discussion

For all formulations a tablet hardness of roughly 200 N was aspired in order not to falsify the drug release by an overdone tablet hardness but to guarantee a good mechanical tablet stability.
As shown in **table 1** the tramadol formulation shows excellent flow characteristics, easy tablet manufacture and prominent mechanical tablet properties. The drug dissolution profile reaches approx. 90 % after 16 h **(figure 1).**

	Tramadol K-SR (1:1.5)	Diltiazem K-SR (1:1.5)	Diclofenac K-SR (1:1)	Diclofenac K-SR (1:1.5)
Tramadol	100	–	–	–
Diltiazem	–	120	–	–
Diclofenac	–	–	100	100
Kollidon® SR	150	180	100	150
Aerosil 200	2.5	3	3.4	3.4
Magnesium stearate	1.25	1.5	3	3
Flow time [s]	9.2	15.5	20.9	21.5
Angle of repose [°]	24.6	29.0	26.6	26.1
Compression force [kN]	12.6	7.96	7.88	7.02
Hardness [N]	211	217	195	229
Friability [%]	< 0.01	0.01	0.09	0.07

ExAct
Excipients & Actives for Pharma

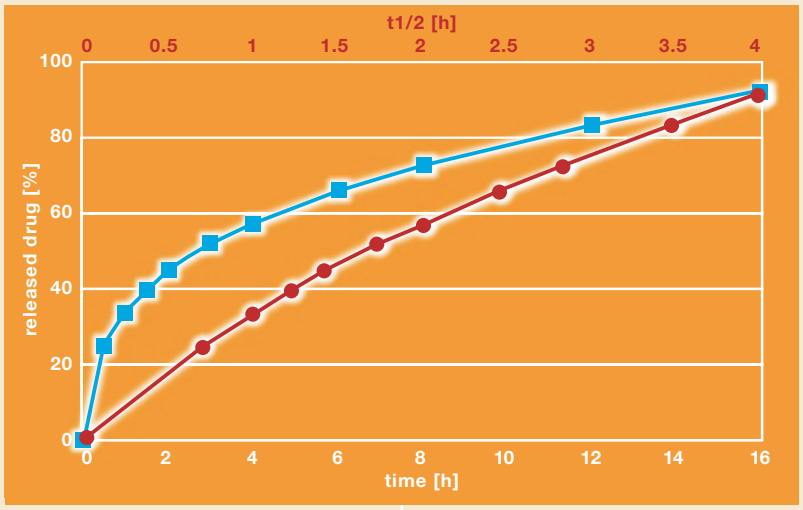
The √t-charts (red lines) demonstrate good linearity for the release profile.

Like the tramadol formulation Kollidon® SR-based diltiazem tablets were also kept at a 1:1.5 ratio, which resulted in acceptable powder properties. The required tablet hardness of 200 N has already been achieved with a compression force < 10 kN. The release behavior of diltiazem **(figure 2)** depicts nearly the same image as it could be found for the tramadol formulation.

Although the angle of repose for a diclofenac-Kollidon® SR (1:1) composition is acceptable, the flow time reaches a critical limit. An increase of the Kollidon® SR admixture up to 1:1.5 gives no substantial improvement of the powder characteristics, but raises the mechanical performance. This 1:1.5 ratio is not sufficient to mask the known bad flow properties of diclofenac, but considerably intensifies the sustained release characteristic **(figure 3).**

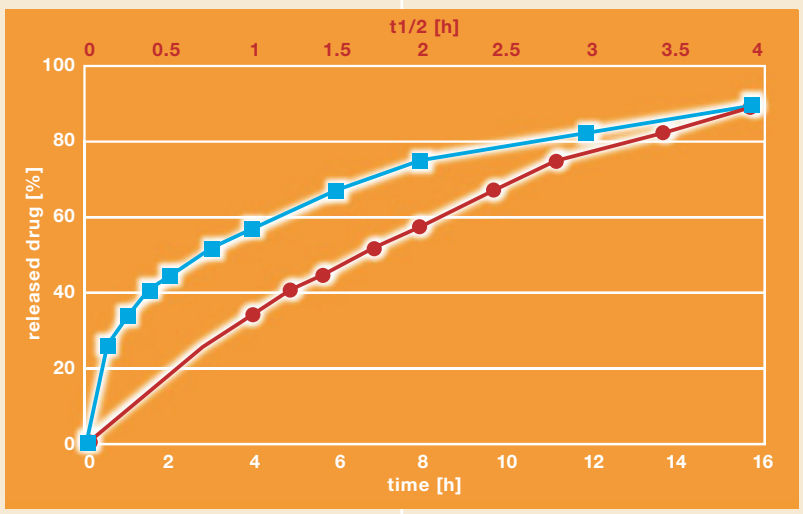
The poor solubility of diclofenac compared to the aforementioned drugs explains the reduced release rate while the Kollidon® SR ratio is kept constant.

To modify the release profile, apart from varying the Kollidon® SR ratio, combinations together with other excipients are also practicable. In no case any drug incompatibility occurred with Kollidon® SR-based matrix tablets.



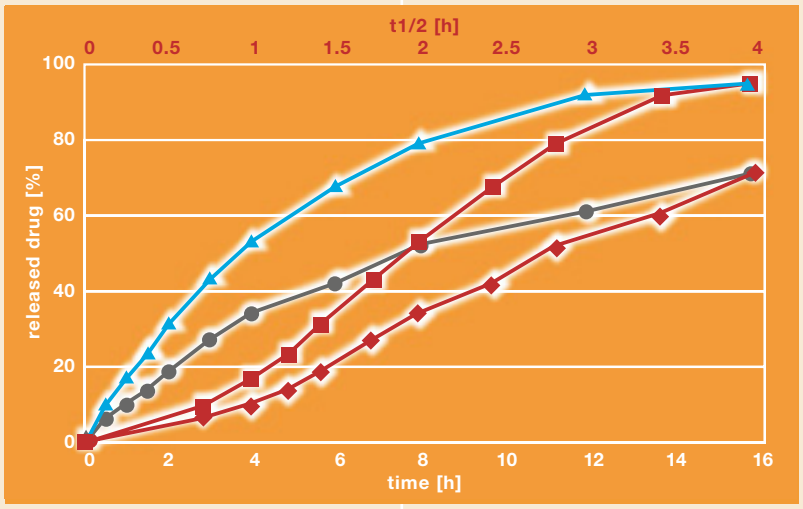
Release profile of a Kollidon® SR-based controlled release formulation of diltiazem-HCl ***(Figure 1)***

■ **Diltiazem 120 mg K-SR 180 mg**
● **Diltiazem 120 mg K-SR 180 mg/√t**



Release profile of a Kollidon® SR-based controlled release formulation of tramadol-HCl ***(Figure 2)***

■ **Tramadol 100 mg K-SR 150 mg**
● **Tramadol 100 mg K-SR 150 mg/√t**



Release profile of a Kollidon® SR-based controlled release formulation of diclofenac-Na ***(Figure 3)***

▲ **Diclofenac 100 mg K-SR 100 mg**
● **Diclofenac 100 mg K-SR 150 mg**
■ **Diclofenac 100 mg K-SR 100 mg/√t**
◆ **Diclofenac 100 mg K-SR 150 mg/√t**

› References
[1] M. J. Vasquez; Drug Dev. Ind. Pharm., 18; 1355, 1992.
[2] U. Gundert-Remy, "Oral controlled release products" WVG, Stuttgart, 1990.
[3] D. J. Chetty; Pharm. Tech. Eur. November, 1994.

› Conclusions

› Kollidon® SR can easily be applied for controlled release properties by direct compression.

› It favors the development and manufacture of sustained release tablets by its high dry binding capacity and the superb flow properties.

› This excipient offers a reliable sustained release characteristic independent of the drug used.

ExAct
Excipients & Actives for Pharma

Kollicoat® EMM 30 D

Coatings on pellets using fluidized bed and Huettlin coaters.

S. Scheiffele, K. Kolter (BASF), D. Kovacevic, G. Schepky (Pharma Technology, 72488 Sigmaringen)

› Purpose

Ethyl acrylate-methyl methacrylate (EMM) is a well-known polymer for the manufacture of sustained release dosage forms **[1].** Kollicoat® EMM 30 D exhibits a certain level of tackiness, which limits the coating process **[2].** This study describes trials in different coaters and with different batch sizes.

› Methods

Materials

Kollicoat® EMM 30 D, Sicovit® Red 30, Kollidon® 30, Kollidon® VA 64 (BASF AG), propranolol-HCl, ibuprofen (BASF AG), talc (Riedel de Haen), titanium dioxide (Kronos), Pharmacoat 603 (Shin-Etsu), Avicel PH 105/101 (Lehmann & Voss), Granulac (Meggle).

Diagram of a Huettlin coater. Huettlin Kugelcoater is a universal fluid bed unit suitable for aqueous and organic processes such as drying, granulation, mixing, coating, microencapsulation and layering, as well as hot melt granulation and coating.

Apparatus

Corundum disc mill (Fryma Maschinenbau GmbH), fluid bed coater (Aeromatic-Fielder, Huettlin), dissolution tester (Pharmatest Apparatebau), Spheronizer (Heller Labortechnik), sieve (Alexander), blender (Diosna).

Spray suspension

First the pore former (Avicel PH 105, Pharmacoat 603) is dissolved or suspended in the given amount of water. Then the calculated amount of Kollicoat® EMM 30 D is added. Finally the homogenized amount of pigment suspension (Kollidon® 30, Sicovit® Red 30, titanium dioxide, talc) is carefully stirred in **(table 2).**

Pellet formulations (Table 1)

	Ibuprofen	Propranolol
Active	60.00	30.00
Avicel PH 101	37.50	46.70
Kollidon® VA 64	2.50	2.50
Granulac 230	–	20.80
Total	100.00	100.00

Coating formulations (Table 2)

	Ibuprofen	Propranolol
Kollicoat® EMM 30 D	32.50	39.30
Avicel PH 105	4.50	–
Pharmacoat 603	0.75	–
Water	47.25	37.91
Kollidon® 30	0.50	0.50
Sicovit® Red 30	0.50	0.50
Titanium dioxide	0.50	–
Talc	3.50	4.72
Pharsil 21046 VP	–	7.07
Water	10.00	10.00
Total	100.00	100.00

Process parameters (Table 3)

	Ibuprofen	Propranolol
Inlet air temperature	65 °C	40–45 °C
Outlet air temperature	41–42 °C	28–30 °C
Spray rate	12 g/min	7–11 g/min

Coating process

The coating was applied in a fluidized bed coater (Aeromatic Strea 1 and MP 1, Huettlin Kugelcoater HKC 5) on pellets (ibuprofen, propranolol-HCl) **(table 3).**

› Methods

The dissolution rates at different coating weights and the quality of the coated pellets were determined.

› Results and Discussion

The propranolol-HCl pellets coated in a fluidized bed coater demonstrated very similar release characteristics independently of the size of the batch.

As can be seen from **figure 1,** the retard pellets produced in a large batch (MP 1) have a very slightly slower release rate than the pellets from the small batch (Strea 1) that can be explained by their more homogeneous and even film coating. The reproducibility of the formulation used in the fluidized bed coater is also very good, as can be seen in **figure 2.**

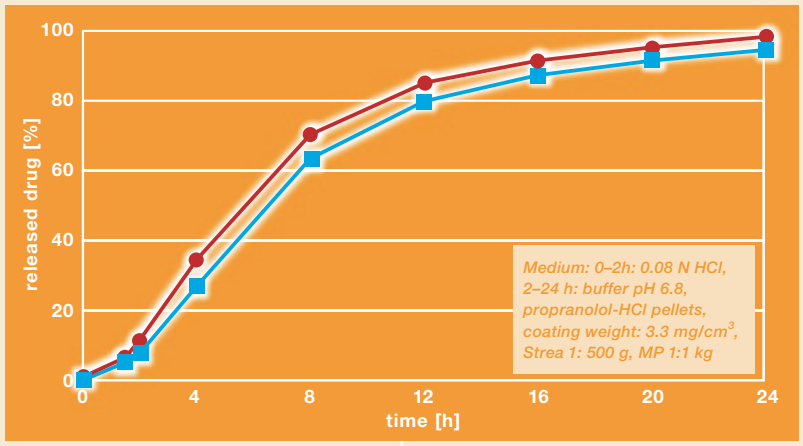
ExAct
Excipients & Actives for Pharma

While the conventional fluidized bed process can be scaled up without affecting the reproducibility of the formulations or the release rate of the pellets, considerable differences are found in the pellets produced in the Huettlin coater. The difference in film quality is clearly visible in **figures 3 and 4.** The pellets produced in the Huettlin coater have a much smoother surface than the traditionally coated pellets, which delay drug release more strongly **(see figure 5).**

Both the good reproducibility and the small influence of subsequent tempering of the coated pellets can be seen clearly from **figure 6.** The smooth film obtained in this coating process makes it unnecessary to temper the pellets afterwards.

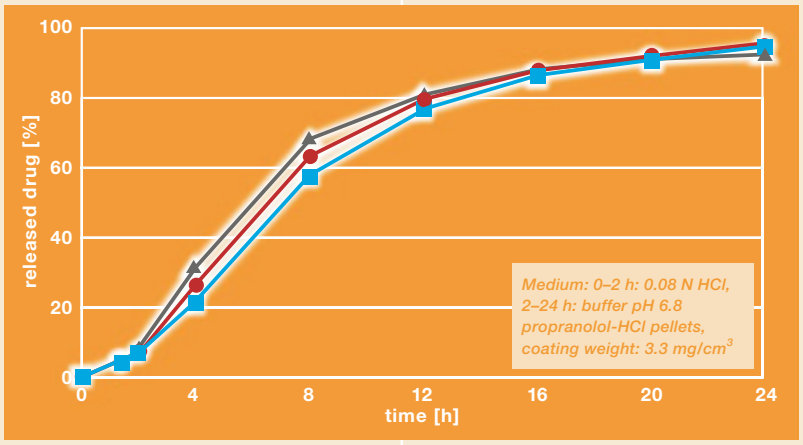
› **References**
[1] T. C. Rock , D. Flick, K. Kolter, Proc. of the 27th International Symposium on Controlled Release of Bioactive Materials, Paris, 7–13 July 2000, 8406.
[2] H. Erdmann, S. Scheiffele, G. Schepky and K. Kolter, Proc. of the 3rd World Meeting APV/APGI, Berlin, 3–6 April 2000, p. 131.

› **Conclusions**
› The formulations tested demonstrate good reproducibility both in the conventional fluidized bed coater and in the Huettlin Kugelcoater.
› The fluidized bed process can be scaled up without much effect on the film quality and the release rate.
› The Huettlin Kugelcoater gives more homogeneous filmcoatings and slower release rates than fluidized bed machines.
› It is not necessary to temper the coated pellets.



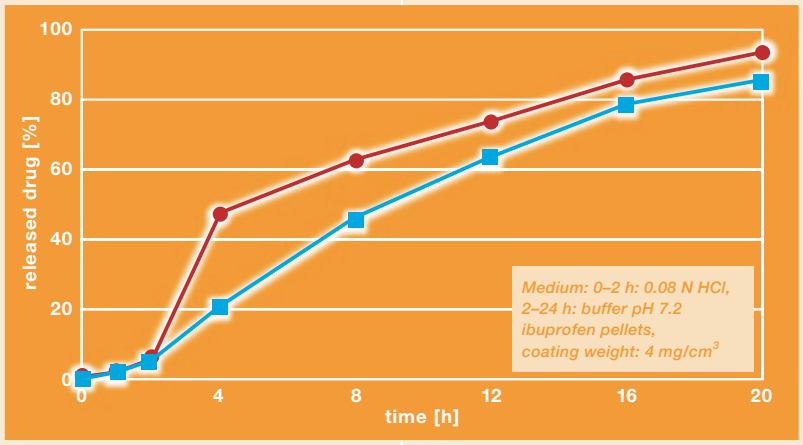
Comparison of pellets sprayed in Aeromatic types Strea 1 and MP 1 ***(Figure 1)***

■ MP 1
● Strea 1



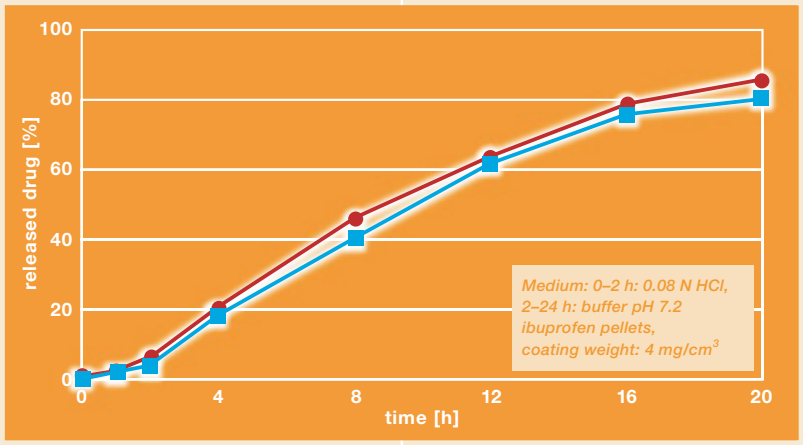
Reproducibility of the batches produced in the Aeromatic MP 1 ***(Figure 2)***

● MP 1_1
■ MP 1_2
▲ MP 1_3



Comparison of the pellets sprayed in the Aeromatic type Strea 1 and Huettlin coaters ***(Figure 3)***

■ Huettlin
● Strea 1



Effect of curing pellets coated in the Huettlin Kugelcoater ***(Figure 4)***

■ with curing (40 °C/24 h)
● without curing

ExAct
Excipients & Actives for Pharma

Kollicoat® IR

Binding properties of the new polymer.

K. Kolter

› Purpose

Kollicoat® IR (polyvinyl alcohol polyethylene glycol graft copolymer) was designed as an instant release film-forming agent. In prin--ciple, water-soluble polymers can act as wet binders in tablet manufacturing. The aim of this study was to investigate and assess its wet binding properties by comparison with well-known binders.

› Methods

Materials

Polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat® IR, BASF Aktiengesellschaft), copovidone (Kollidon® VA 64, BASF Aktiengesellschaft), HPMC 3 mPas (Pharmacoat 603, Shin-Etsu), ascorbic acid powder (BASF Aktiengesellschaft), corn starch (C-Pharm, Cerestar), lactose (Sachelac 80, Meggle), microcrystalline cellulose (Avicel PH 101, FMC), crospovidone (Kollidon® CL, BASF Aktiengesellschaft), magnesium stearate (Bärlocher).

Placebo powder blend

Placebo granules Kollicoat® IR

Methods

Kollicoat® IR, Kollidon® VA 64 and HPMC 3 mPas were tested in two formulations, both at a binder level of 3 %.

The tablets were compressed on a Korsch PH 106 rotary press equipped with Compression Research System at 10, 18 and 25 kN.

Settings of fluid bed granulation	(Glatt GPC G3)
Concentration binder solution:	7.5
Inlet air temperature:	50 °C
Spray rate:	30 g/min
Outlet air temperature:	approx. 27 °C
Granulation time:	approx. 20 min
Settings of mixer granulation	**(Stephan mixer)**
Concentration binder solution:	15 %
Propeller speed:	800 rpm
Granulation time:	12 mm
Sieve size:	0.8 mm

› Results

The granulation efficiency can be demonstrated explicitly by means of the mean particle size and flow behavior. All binders tested, Kollicoat® IR, Kollidon® VA 64 and HPMC 3 mPas, greatly increased the mean particle size from 67 resp. 92 µm of the ungranulated powder blend to 483–545 resp. 355–398 µm in mixer granulation. Simultaneously angle of repose decreased from 49.7° resp. 40.0° to 31.9–34.0° and the non-flowing powder was transformed into free-flowing granules. Agglomeration was also apparent in fluid bed granulation. However, as expected, particle size in fluid bed granulation (148–189 µm) was lower when compared to granulation in a mixer, and angle of repose slightly higher due to an increased porosity and rougher surface structure **(figure 1).** Both, in mixer and fluid bed granulation, Kollicoat® IR showed excellent agglomeration activity comparable to the well-known binders Kollidon® VA 64 and HPMC 3 mPas.

Table 1: Tablet formulations

	Placebo tablets	Ascorbic acid tablets
Ascorbic acid	–	50.0 mg
Corn starch	230.0 mg	–
Lactose	230.0 mg	130.0 mg
MCC	–	130.0 mg
Binder	15.0 mg	10.0 mg
Kollidon® CL	22.5 mg	10.0 mg
Magnesium stearate	2.5 mg	2.0 mg
Total	500.0 mg	332.0 mg
Diameter	12 mm	10 mm
Batch size	1.50 kg	1.33 kg

Table 2: Powder characteristics of placebo granules

	Powder blend	Kollicoat® IR	Kollidon® VA 64	HPMC 3 mPas
Loss on drying	–	6.6 %	6.8 %	7.1 %
Angle of repose	49.7°	32.4°	34.0°	33.9°
Flow time	blocking	8.9 sec	8.7 sec	8.7 sec
Mean particle size (D[4,3]-value)	67 µm	545 µm	497 µm	483 µm
Bulk density	0.57 g/ml	0.47 g/ml	0.48 g/ml	0.50 g/ml

Table 3: Peroxide formation of Kollicoat® IR

storage time	storage conditions	peroxide level (meq/kg)
0 months	–	1
3 months	25 °C/60 % r. h.	< 1
3 months	40 °C/75 % r. h.	< 1
6 months	25 °C/60 % r. h.	< 1
6 months	40 °C/75 % r. h.	< 1
12 months	25 °C/60 % r. h.	4
12 months	40 °C/75 % r. h.	1
18 months	25 °C/60 % r. h.	3
18 months	40 °C/75 % r. h.	1

ExAct
Excipients & Actives for Pharma

Table 4: Powder characteristics of ascorbic acid granules

	Powder blend	Kollicoat® IR		Kollidon® VA 64		HPMC 3 mPas	
		mixer	fluid bed	mixer	fluid bed	mixer	fluid bed
Loss on drying	–	3.0 %	2.7 %	2.3 %	2.9 %	2.2 %	3.1 %
Angle of repose	40°	32.6°	34.3°	31.9°	35.8°	32.2°	35.4°
Flow time	blocking	8.2 sec	7.8 sec	7.4 sec	8.2 sec	8.6 sec	7.8 sec
Mean particle size (D[4,3]-value)	92 µm	397 µm	162 µm	355 µm	148 µm	398 µm	189 µm
Bulk density	0.45 g/ml	0.57 g/ml	0.43 g/ml	0.57 g/ml	0.43 g/ml	0.57 g/ml	0.34 g/ml

The formation of granules is promoted by the excellent film-forming properties of the polymers. A binder should not only improve the flow properties but also improve compressibility and tablet properties. The hardness-compression force profiles clearly indicate that all binders tested have good binding power. Kollicoat® IR was particularly effective in mixer granulation of ascorbic acid tablets, where it outperformed Kollidon® VA 64 and HPMC 3 mPas (73 to 59 and 63 N at 18 kN compression force). However, in the placebo tablets Kollidon® VA 64 resulted in slightly harder tablets **(figure 2 and 3).** A comparison of the ejection forces of fluid bed granulated ascorbic acid tablets revealed lower values for Kollicoat® IR. Thus, this polymer promotes the lubrication effect of magnesium stearate **(figure 4).** The disintegration times of the tablets are correlated with the dissolution speed and viscosity of the binders used. Whereas Kollicoat® IR and Kollidon® VA 64 showed a low viscosity of 115 mPas and 49 mPas in a 20 % solution and therefore short disintegration times of 1–2 min, HPMC even in the lowest viscosity grade (800 mPas/20 % solution) prolonged disintegration up to 3–4 min **(figure 5).** A binder particularly for low dosed and oxygen sensitive drugs should initially have a low peroxide content and should not generate peroxides upon storage. The peroxide levels of Kollicoat® IR remained very low even after 18 months at 40 °C/70 % r. h. In order to show that there is no binder-related degradation of ascorbic acid a stability study was initiated.

Particle size distribution of placebo granules ***(Figure 1)***

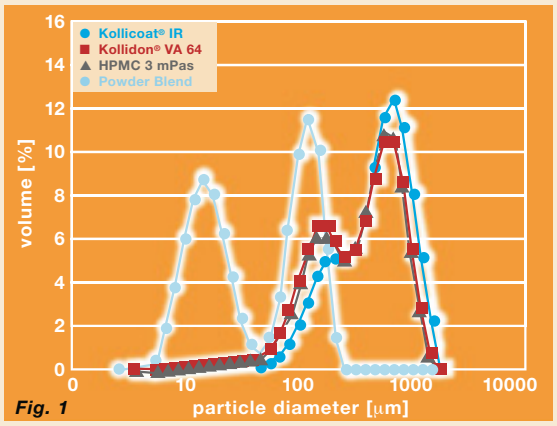


Fig. 1

Hardness-compression force profile of placebo tablets (mixer granulation) ***(Figure 2)***

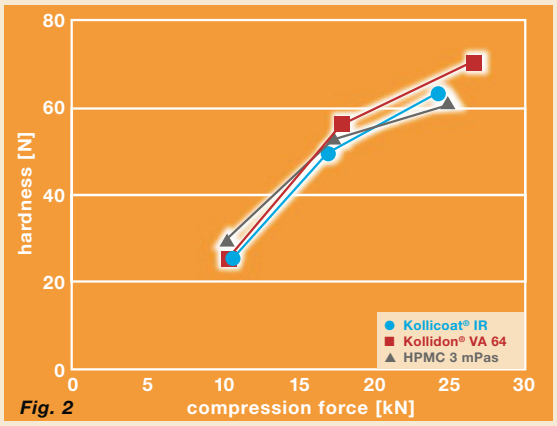


Fig. 2

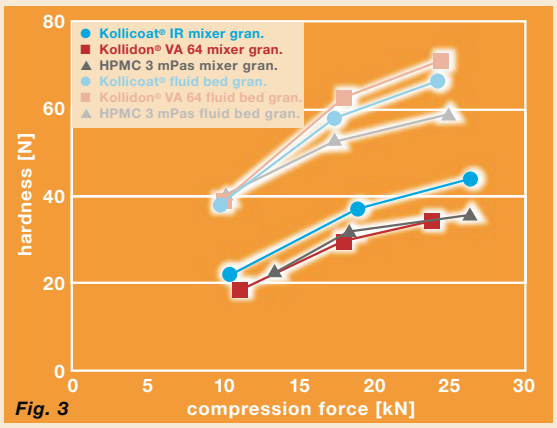


Fig. 3

Hardness-compression force profile of ascorbic acid tablets ***(Figure 3)***

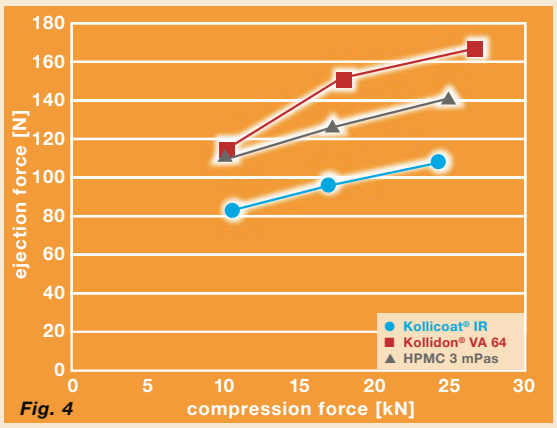


Fig. 4

Ejection forces of ascorbic acid tablets (fluid bed granulation) ***(Figure 4)***

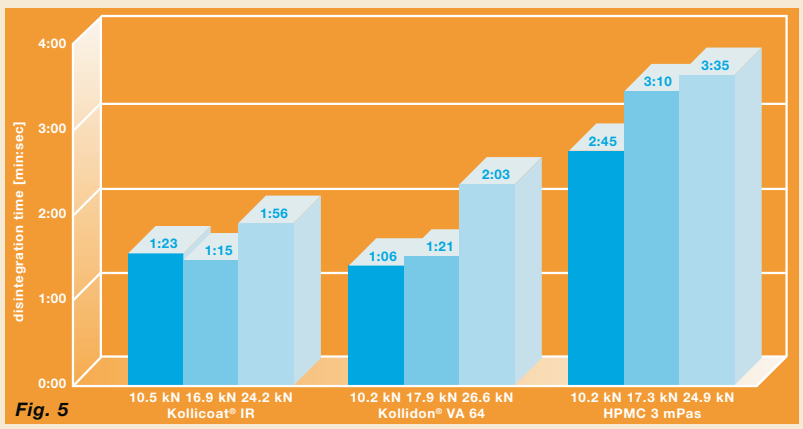


Fig. 5

Disintegration of placebo tablets ***(Figure 5)***

› Conclusions

› Kollicoat® IR exhibited excellent binding properties in wet granulation (mixer and fluid bed).

› As a binder Kollicoat® IR is characterized by ● good flowability of the granules ● high tablet hardness ● low ejection forces ● short disintegration times.

› Due to the low peroxide level it is highly suitable for low dosed and oxygen sensitive drugs.

ExAct
Excipients & Actives for Pharma

Presentation

BASF Development Pharma Ingredients.

T. Steenpaß, T. C. Rock, K. Kolter

You are probably familiar with this famous rhetorical question of A.T. Florence, which expresses the fact that new excipients are relatively rare. Despite the fact that the development of a new excipient is a very time- and cost-consuming process, BASF has established the strategy of differentiating itself from competitors by continuously developing new excipients and active formulations. These new materials offer pharmaceutical companies opportunities for new, innovative drug delivery systems. Furthermore, drug quality and safety are enhanced.

Since 1996, the following products have been launched: Kollicoat® MAE 30 DP, Kollicoat® MAE 100 P, Kollicoat® EMM 30 D, Ludipress® LCE, Kollidon® SR, Kollicoat® SR 30 D and Kollicoat® IR.

Furthermore, numerous new products are in our R&D pipeline. Of course, improvement of our existing products is an ongoing objective. This applies both to excipients and actives, where we are looking for new formulations with attractive benefits.

Our pharma ingredients lab is not only responsible for development issues but also for application technology. We continuously try to find new applications for our excipients, develop and optimize drug formulations, optimize pharmaceutical manufacturing processes and solve any problems you may encounter. With these activities we aim to serve you in an optimal manner.

In order to optimize coordination with you, our facility is equipped just like a pharmaceutical development department, with modern machinery that is suitable for running all the processes of a state-of-the-art drug manufacturing plant. Additionally, we utilize the capabilities of BASF in terms of analytics and physico-chemical characterization. However, the key factor to success is our personnel and we heavily rely on motivated, knowledgeable and well-trained staff.

We will continue to work hard in order to develop new pharmaceutical excipients and active formulations to provide you with even more tools for new drug delivery systems.

BASF – Innovation in Pharma Ingredients

Pharma Ingredients development group

ExAct
Excipients & Actives for Pharma

News

Caffeine may prevent skin cancer.

Treating the skin with caffeine has been shown to prevent skin cancer in laboratory studies conducted at the Susan Lehman Cullman Laboratory for Cancer Research at Rutgers, The State University of New Jersey.

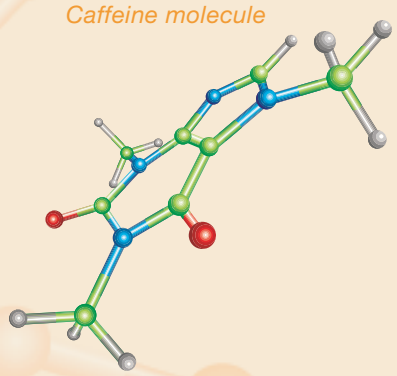
It has been known for some time that skin cancer is caused predominantly by sunlight. The authors, a group that included Conney and a team of other researchers in the laboratory, explained that the use of sunscreens has resulted in a decrease of the risk of skin cancers, but that there is a need to identify additional approaches for skin-cancer prevention in individuals previously exposed to high levels of sunlight.

The research team, all members of the school's Department of Chemical Biology, studied a special strain of hairless mice that had been exposed to ultraviolet B radiation twice weekly for 20 weeks. This put the mice at risk for tumor formation and skin cancer. Subsequent to exposure, the researchers applied caffeine and epigallocatechin gallate (EGCG), two of the components of green tea, topically to the skin. Both caffeine and EGCG significantly inhibited cancer formation in the mice.

Although the study showed that most of the positive effects were true for both of these substances, caffeine has an advantage over EGCG: EGCG is chemically less stable; thus, there could be a problem in applying it topically. Conney said that a previous study conducted in the laboratory dealt with caffeine taken orally.
The caffeine was provided in the drinking fluid for the mice and the researchers found that it inhibited ultraviolet radiation-induced tumors and cancers in this case as well.

Conney cites the advantages of using direct skin application over oral administration, pointing to the ability to administer more highly concentrated and larger overall dosages. “Whether you can give enough orally to be effective in humans is not known”, said Conney. “And whether people could ingest the necessary amount without becoming hyperactive is also a real question mark.” The published study also reported the highly selective action of both caffeine and EGCG in destroying cancer cells. Adjacent normal skin cells were not affected. “The discovery of this selectivity was very exciting”, said Conney. “Also, in our study, it didn’t matter whether the tumors were benign or malignant; cells of both types were destroyed whilst normal cells remained unaffected.” The study suggests further research is needed to determine whether or not topical application of these agents would be effective in humans.

Caffeine molecule



New Media

Products for the food and pharmaceutical industry.

Technical Information
BASF has been involved in the field of health and nutrition for some 20 years. During this time we have developed to become an important partner to the pharmaceutical and food industries. Today, BASF offers a wide range of high-quality products and services worldwide in the areas of health and nutrition.

Our extensive product range comprises vitamins, vitamin blends in oil and in powder form and carotenoids, but also polyunsaturated fatty acids, colorants and numerous other specialties. This book/CD ROM is intended to meet the needs of our customers for a comprehensive, up-to-date handbook with a clear layout providing quick access to information.

It covers all the main technical data on BASF vitamins, carotenoids and other nutritional ingredients for the pharmaceutical and food industries and can be ordered with the attached reply card.

ExAct
Excipients & Actives for Pharma

Preview

Gastric resistance of Kollicoat® MAE 100 P.

Kollicoat® MAE 100 P is a redispersible powder of methacrylic acid copolymer type C which is manufactured by spray-drying the respective dispersion marketed as Kollicoat® MAE 30 DP.
The major advantage of Kollicoat® MAE 100 P compared to other products is that neutralization with sodium hydroxide is not necessary as it is already partly neutralized.

ExAct No. 11 will include sample formulations and a comparison of the two Kollicoat® MAE grades regarding their gastric resistance, spraying behavior and viscosity.

Should you require information in advance, please contact your local BASF subsidiary or one of our regional marketing offices.

For technical reasons, the article on Kollicoat® SR 30 D which was announced in ExAct No. 9 could not yet be published. This article will appear in one of the forthcoming editions.

Calendar

18th to 23rd July, 2003
30th International Symposium on Controlled Release of Bioactive Materials
Glasgow, Scotland

27th to 29th October, 2003
CPhI Worldwide
Frankfurt*, Germany

23rd to 30th October, 2003
AAPS (American Association of Pharmaceutical Scientists) Annual Meeting
Salt Lake City*, USA

4th to 9th September, 2003
World Congress of Pharmacy and Pharmaceutical Sciences, 63rd Congress of FIP
Sydney, Australia

26th to 28th September, 2003
5th Central European Symposium on Pharmaceutical Technology and Biotechnology
Ljubljana, Slovenia

29th May to 3rd June, 2004
Pharmaceutical Sciences World Congress (PSWC2004)
Kyoto, Japan

Summer 2004
31st International Symposium on Controlled Release of Bioactive Materials
Orlando*, USA

* BASF will be represented.

Contact

Please contact your local BASF subsidiary or one of the following regional centres:

Asia
BASF Asia Pacific Regional HQ
Pharma Solutions,
Dr. Danilo Mercado
BASF South East Asia Pte Ltd
9/F., Suntec Tower Three
7 Temasek Boulevard
Singapore
Fax: +65/430 9812

Europe
BASF Aktiengesellschaft
MEE/HP-Rheincenter,
Mr. Peter Hoffmann
D-67056 Ludwigshafen
Germany
Fax: +49/621 60 76940

NAFTA
BASF Corporation
Pharma Solutions,
Mr. Patrick Glaser
3000 Continental Drive-North
Mount Olive, NJ 07828-1234
USA
Fax: +1/973 426 5355

South America
BASF S.A.
Human Fine Chemicals,
Mr. Giancarlo Farias Marinho
Estrada Samuel Aizemberg, 1707
09851-550 São Bernardo do Campo – SP
Brazil
Fax: +55/11 43 43 22 55

Or visit our website: www.pharma-solutions.basf.com

Please write in block letters. Thank you.

Name

Title

Company

Department

Address

City/State

Zip/Country

Phone

Fax

Please apply postage stamp.

Reply card

BASF Corporation
Pharma Ingredients
Attn: Patrick Glaser
Mail stop 2-050
3000 Continental Drive-North
Mount Olive,
New Jersey 07828-1234
USA

Please write in block letters. Thank you.

Name

Title

Company

Department

Address

City/State

Zip/Country

Phone

Fax

Please apply postage stamp.

Reply card

BASF Corporation
Pharma Ingredients
Attn: Patrick Glaser
Mail stop 2-050
3000 Continental Drive-North
Mount Olive,
New Jersey 07828-1234
USA

Please write in block letters. Thank you.

Name

Title

Company

Department

Address

Town

Country

Phone

Fax

Please apply postage stamp.

Reply card

BASF
Aktiengesellschaft
E-MEE/HP – Rheincenter
Pharma Solutions
Attn: Peter Hoffmann
67056 Ludwigshafen

Please write in block letters. Thank you.

Name

Title

Company

Department

Address

Town

Country

Phone

Fax

Please apply postage stamp.

Reply card

BASF
Aktiengesellschaft
E-MEE/HP – Rheincenter
Pharma Solutions
Attn: Peter Hoffmann
67056 Ludwigshafen

Please write in block letters. Thank you.

Name

Title

Company

Department

Address

Town

Country

Phone

Fax

Please apply postage stamp.

Reply card

BASF
Aktiengesellschaft
MEM/PE – D 205
Attn: Dr. Hubertus Folttmann
67056 Ludwigshafen

Please write in block letters. Thank you.

Name

Title

Company

Department

Address

Town

Country

Phone

Fax

Please apply postage stamp.

Reply card

BASF
Aktiengesellschaft
MEM/PE – D 205
Attn: Dr. Hubertus Folttmann
67056 Ludwigshafen

Please send me the following information:

- ☐ Technical Information on Ludipress® LCE.
- ☐ Technical Information on Kollidon® SR.
- ☐ Technical Information on Kollicoat® EMM 30 D.
- ☐ Technical Information on Kollicoat® IR.
- ☐ Products for the Food and Pharmaceutical Industry – Technical Information (book).
- ☐ Products for the Food and Pharmaceutical Industry – Technical Information (CD-ROM).
- ☐ **I would like to receive *ExAct* in future.**
- ☐ "Generic Drug Formulations" ringfile with 600 drug formulations.
- ☐ "Kollidon® – Polyvinylpyrrolidone for the pharmaceutical industry" (book).
- ☐ "Functions and Applications of BASF Pharma Excipients" "Generic Drug Formulations" and "Kollidon®" (CD-ROM)
- ☐ "Functions and Applications of BASF Pharmaceutical Excipients" (booklet)
- ☐ CD-ROM on Contract Manufacturing.
- ☐ _____

_____

Please send me the following information:

- ☐ Technical Information on Ludipress® LCE.
- ☐ Technical Information on Kollidon® SR.
- ☐ Technical Information on Kollicoat® EMM 30 D.
- ☐ Technical Information on Kollicoat® IR.
- ☐ Products for the Food and Pharmaceutical Industry – Technical Information (book).
- ☐ Products for the Food and Pharmaceutical Industry – Technical Information (CD-ROM).
- ☐ **I would like to receive *ExAct* in future.**
- ☐ "Generic Drug Formulations" ringfile with 600 drug formulations.
- ☐ "Kollidon® – Polyvinylpyrrolidone for the pharmaceutical industry" (book).
- ☐ "Functions and Applications of BASF Pharma Excipients" "Generic Drug Formulations" and "Kollidon®" (CD-ROM)
- ☐ "Functions and Applications of BASF Pharmaceutical Excipients" (booklet)
- ☐ CD-ROM on Contract Manufacturing.
- ☐ _____

_____